

Graham Roberts Study protocol

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BMJ Open Graham Roberts Study protocol: first 'trials within cohort study' for bladder cancer

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ABSTRACT

Introduction Given the need for more bladder cancer research and the recently observed advantages of introducing the trials within cohort (TwicCs) design, the set-up of the Graham Roberts Study (Roberts Study) will provide valuable infrastructure to answer a wide variety of research questions of a clinical, mechanistic, as well as supportive care nature in the area of bladder cancer.

Methods Using the TwicCs design, we will recruit patients aged 18 or older who are willing and able to provide signed informed consent and have a diagnosis of new or recurrent bladder cancer into this prospective cohort study. All patients must have a basic understanding of the English language. The following questionnaires will be collected at baseline and every 12 months subsequently: Functional Assessment of Chronic Illness Therapy for Bladder Cancer, the Functional Assessment of Chronic Illness Therapy-Fatigue, the Patient Health Questionnaire-9, the standardised instrument for a generic health status (EQ-5D-5L), a Short Questionnaire to Assess Health-Enhancing Physical Activity and the Hertfordshire Short Questionnaire to Assess Diet Quality.

Ethics and dissemination Due to the nature of this study, we obtained full ethical clearance from the London—Fulham Research Ethics Committee (17/L01975). All participants must provide full informed consent before recruitment onto the study. The results of this study will be published in peer-reviewed journals and data collected as part of the study will be made available to potential collaborators on an application basis.

BACKGROUND

Bladder cancer is the seventh most common cancer in the UK, with about 10,400 patients diagnosed annually¹; about 50% of patients will survive their cancer for 10 years or more after diagnosis. For the majority of patients, the disease remains indolent following initial treatment, and invasive and burdensome surveillance is required to mitigate the high risk of recurrence.² However, there is proportionally less research into bladder cancer compared with breast, prostate or kidney

Strengths and limitations of this study

- First trials within cohort (TwicCs) study design for bladder cancer.
- TwicCs design generates a wide variety of research opportunities with limited risk to patients.
- The non-interventional nature of this study means that patient participation may not benefit patients' bladder cancer prognosis or quality of life.

cancer.³ To provide the most efficient and high impact research strategy for patients with bladder cancer in the UK, we have established a prospective cohort study of newly diagnosed patients with bladder cancer to allow research that can efficiently address clinical, mechanistic, as well as supportive care-related questions.

The design of this bladder cancer cohort study is similar to the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation,⁴ which is based on the trials within cohort (TwicCs) design introduced by Relton *et al*⁵ at the University of Sheffield in 2010. It is the first TwicCs design study in the area of bladder cancer.

The use of TwicCs has grown substantially in the last few years, with several new initiatives in the UK. TwicCs, originally introduced as cohort multiple randomised controlled trial (RCT) design, was introduced to address the problems associated with existing approaches for trials informing routine clinical practice.⁵ Such shortcomings relate to recruitment, ethics, patient preferences and treatment comparisons. At least six TwicCs studies are currently ongoing in the UK.⁶

The Roberts Study will serve as a facility for multiple trials and follows the TwicCs design.

The main objectives of the Graham Roberts Study (Roberts Study) are:



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- ▶ To create a prospective cohort study of well-characterised patients with bladder cancer, which provides the opportunity to conduct a variety of observational studies.
- ▶ To create the infrastructure for future RCTs that will allow more efficient recruitment using patient-centred informed consent.

METHODS/DESIGN

TwicCs design

The TwicCs design can be described as follows: initially, an observational cohort of patients with the condition of interest is recruited and their characteristics and outcomes measured longitudinally. Then, for each subsequent RCT, eligible patients from the cohort are identified using the collected longitudinal information. Eligible patients are randomised, and those selected are offered the trial intervention. Comparisons are then drawn between the outcomes of the randomly selected patients and the eligible patients not randomly selected, that is, those receiving usual care. This process can be repeated for future RCTs within the cohort.⁵

Longitudinal observational studies are characterised by the recruitment and regular follow-up of a large cohort of patients. The TwicCs design, however, is unique as all patients within the cohort consent at the outset to provide data to further investigate the benefits of treatments or interventions for the condition of interest. The study design holds capacity to develop multiple RCTs using patients from the same cohort. Indeed, the similarity of this approach to patient-centred informed consent offers a solution to the ethical criticisms of the traditional randomised consent designs.⁵

Graham Roberts Study

Patients will be recruited at Guy's and St Thomas' (GSTT) National Health Service (NHS) Foundation Trust, London, UK. All patients will be eligible for the study following their first visit for a new or recurrent bladder cancer diagnosis. Patients with limited understanding of the English language and patients under the age of 18 years are ineligible. Since GSTT NHS Foundation Trust is a referral centre, the Roberts Study will include patients from various secondary and tertiary hospitals located across the UK. Each year, approximately 100 eligible patients visit the Urology Centre of GSTT for bladder cancer management.

All eligible patients who have already undergone diagnostic investigations and been informed about a (highly likely) bladder cancer will receive detailed written information about the Roberts Study while attending the Urology Centre for their initial appointment. They will be scheduled to see a member of the direct clinical care team and a research nurse/assistant 30 min prior to their first appointment with the consultant (urology or oncology). During this research consultation, the research nurse/assistant will explain the study in detail and written informed consent will be obtained from

those who agree to participate. Such consent will be gained to allow:

- ▶ Participation in the Graham Roberts Study cohort and longitudinal study.
- ▶ The participant to be approached to participate in the intervention arm of any future RCT.
- ▶ The participant to be randomised to the control arm of any future RCT without knowledge of this status.
- ▶ Collection and storage of participants biological samples, including blood, urine and tissue, within the KHP Bladder Cancer Biobank.
- ▶ Linkage and use of participants routinely collected clinical data as recorded in electronic patient records.

At the time of full informed consent, the patients will also be provided with the study baseline questionnaire and asked to complete this at a convenient time.

For those eligible patients who have not yet been informed about their bladder cancer diagnosis at the time of visiting the Urology Centre, detailed written information about the Roberts Study will be provided by a research nurse/assistant after they have met with the consultant. If the patients are not ready to discuss this study in further detail at this point, a follow-up call will be made 1 week later to obtain their consent, if they have agreed to participate. Full written informed consent is subsequently obtained at the patients next clinical appointment.

Data from all patients may be used for observational studies in the Roberts Study, but only those who provide consent for randomisation are eligible for participation in the RCTs within the Roberts Study.

Thus, the TwicCs design is based on an 'asymmetric informed consent'. After recruitment into the Roberts cohort, the randomisation of eligible subjects can be followed by an asymmetric treatment of the two arms; those selected for the experimental arm provide informed consent for the intervention trial, while the data from the control arm are used based on prior broad permission. Hence, the cohort participants are informed about future research within the cohort.

Selection and withdrawal of subjects

Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

- ▶ Appointment for a new or recurrent diagnosis of bladder cancer at GSTT' NHS Foundation Trust.
- ▶ Minimum age of 18 years.
- ▶ Basic understanding of English.

Patients will be identified in multidisciplinary team meetings or in outpatient clinics by the clinical team, in collaboration with the research nurse. Participants have the right to withdraw from the study at any time for any reason. Their routine medical and surgical care will not be affected.

Expected duration of the study and sample size

As this study is an observational prospective cohort study, it is difficult to estimate its duration. We aim to recruit a

minimum of 400 patients over a period of 5 years, though there is no limit to the number of patients needed for a prospective cohort study. Moreover, over time, new research opportunities will develop and potential funding may become available to continue recruitment into the Roberts Study. Patients will be followed up for life through data linkages with Hospital Episode Statistics (HES), the Office for National Statistics (ONS) and electronic patient records.

As this is a prospective cohort study, with no specific primary research question, it is not possible to perform sample size calculations. However, it is still important to consider recruitment rates and response rates to the questionnaires.

Recruitment to the Graham Roberts Study commenced on 23 March 2018. At the point of submission of this protocol (April 2019), 84 patients with bladder cancer had been approached with a patient information sheet, and 72 patients had provided full written informed consent and completed the baseline study questionnaire. At current rates of consent, the authors project the baseline recruitment of 400 patients with bladder cancer to be completed by 31 August 2023. It is expected, however, that recruitment rates will increase as the direct clinical care team and research nurses/assistants become more efficient at identifying and approaching eligible patients. The projected end of recruitment date is therefore set at 31 December 2022. Moreover, ethical clearance is in place to recruit until this date.

Data collection

Within the Roberts Study, various clinical data will be prospectively collected including demographics, tumour characteristics, treatment and CT and MRI imaging data. Clinical data will be captured from electronic medical records, referral letters and annual reports for Public Health England.

Sociodemographic data will include sex, date of birth, age at diagnosis, highest level of education, postal code (to estimate the deprivation index), body mass index and WHO performance status.

The following tumour characteristics will be collected: the TNM classification of malignant tumours, stage, grade, tumour diameter, number of tumours, histology and morphological codes and invasiveness.

Treatment characteristics comprise data on type and timing of treatment given (eg, intravesical instillations,

systemic chemotherapy, radical cystectomy, radiotherapy or other treatments). Additional detailed data, as reported in surgical notes, will be available for those patients with bladder cancer who undergo radical cystectomy. Table 1 illustrates the preoperative, perioperative and postoperative variables which will be collected for this patient subset.

Information on disease progression, recurrence and survival will be collected annually by means of the data linkages with HES, ONS and electronic patient records. We will also collect patient-reported outcome measures (PROMs) by means of validated questionnaires designed to quantify health-related quality of life (QoL) from the patients' perspective. These questionnaires will be given (paper (post) or digital (email or tablet in clinic)) to patients on entry into the cohort (baseline) and every 12 months thereafter with a total follow-up of at least 10 years. It will take about 30 min to fill out the set of questionnaires at each time point.

PROMs will be collected on QoL, fatigue, anxiety and depression, physical activity, dietary habits as well as risk behaviour in terms of known bladder cancer risk factors. Following an assessment of smoking behaviour, alcohol consumption and occupational bladder cancer risk factors, the following validated questionnaires will be used (see online supplementary additional file 1):

- *QoL*: Functional Assessment of Chronic Illness Therapy for Bladder Cancer.⁷
- *Fatigue*: Functional Assessment of Chronic Illness Therapy-Fatigue.⁸
- *Depression*: Patient Health Questionnaire-9.⁹
- *Health*: Standardised instrument for use as a measure of health outcome (EQ-5D-5L¹⁰).
- *Physical activity*: Short Questionnaire to Assess Health-Enhancing Physical Activity.¹¹
- *Assessment of dietary habits*: Short Questionnaire to Assess Diet Quality.¹²

Assessment of safety

As this is a prospective cohort study with no specific interventions, adverse events (AEs) are unlikely to take place. Nevertheless, if filling out questionnaire data should ever result in an AE, it will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 and coded. These will be reported to the Data Monitoring Committee (DMC).

Table 1 Data collection for those participants of the Roberts Study undergoing radical cystectomy

Preoperative	TNM stage, weight, height, BMI, American Society of Anesthesiologists score, previous pelvic surgery, radiation or neoadjuvant chemotherapy
Perioperative	Type of surgery, type of lymphadenectomy, type of urinary diversion, blood loss, duration of surgery, accidental organ injury during surgery
Postoperative	Complications (Clavien-Dindo), reoperations and readmissions within 90 days, length of hospital stay, pT stage, number of excised lymph nodes and number of excised and metastatic lymph nodes

BMI, body mass index.

Given that we see on average about 100 eligible patients per year, we expect to recruit at least 400 patients over a period of 5 years. However, as described above, if more research and/or funding opportunities come up, we will continue recruitment into the Roberts Study.

Patient and public engagement

The development of the Graham Roberts Study was informed in collaboration with patient representatives diagnosed and treated at GSTT' NHS Foundation Trust. Prior to development of the study protocol, a focus group was held to discuss the acceptability of the TwiCs study design and the content of the self-administered questionnaire. Patients of similar bladder cancer diagnoses to those that will be consented onto the study were recruited into this focus group. Based on the patient's experiences and preferences, the Graham Roberts Study design was agreed. Results of the study will be disseminated to the patients through annual newsletters and on a study-specific website for patients.

Direct access to source data and documents

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient in the Roberts Study. Study personnel will enter data from source documents corresponding to a patient's visit into the protocol-specific electronic case report forms (CRFs) in a dedicated, secure data warehouse. Patients will not be identified by name in the study database or on any study documents to be collected by the sponsor (or designee), but will be identified by patient ID numbers.

The database will be safeguarded against unauthorised access with established security procedures; nightly backup of the database and related software files will be maintained. At prespecified junctures of the protocol (eg, production of interim and final reports), data for analysis will be locked and cleaned as per established procedures.

If a correction is required to a CRF, the time and date stamps will track the person entering or updating CRF data and create an electronic audit trail. The chief investigator is responsible for reviewing all information collected on patients enrolled in this study for completeness and accuracy.

To enable evaluations and/or audits from regulatory authorities, the CI agrees to keep records, including the identity of all participating subjects (sufficient information to link records, for example, CRFs and hospital records), all original signed informed consent forms, safety reporting forms, source documents and detailed records of treatment disposition and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports). The records should be retained by the CI according to the International Conference on Harmonisation or local regulations; all study documentation must be retained for 10 years after the study ends.

Quality assurance

Monitoring of this study will be performed to ensure compliance with Good Clinical Practice, and scientific integrity will be managed and oversight retained by the DMC led by Prof Dominique Michaud. The committee will receive notification every 6 months of the interim and total accrual. At the discretion of the chair of the DMC, interim analyses may be scheduled as modifications to the protocol. Additional meetings during the study period may occur at the discretion of the Steering Committee.

The study design, analysis and reporting will follow the recent recommendations for good practice in clinical outcomes assessment by the International Society for Pharmacoeconomics and Outcomes Research.¹³

Data handling

The chief investigator and delegates are responsible for daily cohort management. Data quality will be checked periodically. The following guidelines will be strictly adhered to:

- ▶ Patient data will be anonymised.
- ▶ All anonymised data will be stored on a password-protected encrypted computer.
- ▶ All study data will be stored in line with the Data Protection Act as defined in the King's Health Partners' Clinical Trials Office Archiving SOP.

The data will be stored as outlined in the data management plan.

Insurance/indemnity

The cosponsors King's College London and GSTT' NHS Foundation Trust will provide insurance and indemnity.

DISCUSSION

The Graham Roberts Study is the first of its kind and thus the first TwiCs study for bladder cancer. It generates a wide variety of research opportunities with limited risk to patients. Participation in research involves some loss of privacy. We will do our best to make sure that all personal information gathered for this study is kept private. As this is a non-interventional prospective cohort study, participation may not have a beneficial effect on patients' bladder cancer prognosis or QoL compared with usual care.

The questionnaires to be used are quite detailed and, for the most part, concerns day-to-day activities such as quality and duration of sleep, diet and exercise. The questionnaire does pose some more personal and intrusive questions however, including questions related to symptoms of depression. These questions can be omitted if the participant does not feel comfortable answering them. There is a risk that some participants may be upset by having these questions posed to them. Some participants may prefer to complete the questionnaire themselves, whereas others may prefer to do so with a research assistant. Participants will be fully informed about these potential harms and enabled to make an informed decision regarding participation. We consider that the

potential minor harms are outweighed by the potential benefits of the research.

Future research using the data in this study could lead to medical and scientific products, discoveries, as well as interventions that improve the prevention, diagnosis and treatment of bladder cancer. A benefit for the patients is also the possibility to be part of future RCTs by providing consent for being part of the intervention arm.

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Contributors MVH, FC, HW, CR, CLM and AS designed the study with input from their clinical colleagues (SC, SH, SR, DE, DJ, RTB, SA, KC, MSK) and the biobank coordinator (CG). All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related documents were approved by the London–Fulham Research Ethics Committee as part of gaining Health Research Authority approval (17/LO/1975). After completion of an RCT within the Roberts Study,

all patients—irrespective of participation in the specific study—will receive aggregated results via a newsletter that they can subscribe to at time of initial consent. The results of this study will be published in peer-reviewed journals.

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